REMARKS

In the present communication, Claims 172-189 and 193-197 are currently cancelled. Claims 190 and 191 have been amended. New Claims 206-219 are currently added. As such, Claims 190-192 and 206-219 are currently pending. The Examiner's rejections are as follows:

I) Claims 172, 174, and 195 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Kurn (20020058270) in view of Dai et al. (Genes & Development, vol. 12, pages 2782-2790, 1998);

II) Claims 173, 175-186, 194 and 195 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Kurn, in view of Dai et al., in view of Kacian (U.S. 5,399,491), and further in view of Ginsberg et al.; and

III) Claims 187-193, 196 and 197 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Kurn, in view of Dai et al., in view of Kacian, in view of Ginsberg et al., and further in view of Diegelman et al. (Nucleic Acids Research, vol. 26, pages 3235-3241, 1998).

I. Objections to Claims 172, 174, and 195

The Examiner issued obviousness rejections of Claims 172, 174, and 195 based on Kurn, in view of Dai et al. While Applicants disagree with this rejection, in order to further the prosecution of the present application, without acquiescing to the Examiner's rejection and while reserving the right to prosecute the original or similar claims in the future, Claims 172, 174, and 195 have been cancelled.

II. Objections to Claims 173, 175-186, 194 and 195

The Examiner issued obviousness rejections of Claims 173, 175-186, 194 and 195 based on Kurn, in view of Dai et al., in view of Kacian, and further in view of Ginsberg et al. While Applicants disagree with this rejection, in order to further the prosecution of the present application, without acquiescing to the Examiner's rejection and while reserving the right to prosecute the original or similar claims in the future, Claims 173, 175-186, 194 and 195 have been cancelled.

III. Objections to Claims 187-193, 196 and 197

The Examiner issued obviousness rejections of Claims 187-193, 196 and 197 based on Kurn, in view of Dai et al., and further in view of Kacian, Ginsberg et al., and/or Diegelman et al.

With respect to Claims 187-189, 193, 196 and 197, while Applicants respectfully disagree with these rejections, in order to further the prosecution of the present application, without acquiescing to the Examiner's rejection and while reserving the right to prosecute the original or similar claims in the future, Claims 187-189, 193, 196 and 197 have been cancelled.

Claim 190 is currently amended to an independent claim and to improve clarity and consistency of the claim language. Support for these amendments is provided by previous independent claims 172, dependent claims 173 and 190, and the specification as filed, particularly paragraphs [0522] and [0523] and FIG. 20 of the published application.

Claim 191 is amended to improve clarity and consistency of the claim language.

Claim 190 employs a new and novel composition - *a sense promoter primer* - that was not previously known or used in the art. Further, present Claim 190 provides a new and novel method for using the sense promoter primer in order to amplify target nucleic acid sequences exhibited by one or multiple target nucleic acids in a sample. Some of the various embodiments of the method use a sense promoter primer to yield RNA products that exhibit sequences which are identical to target nucleic acid sequences in the sample.

A sense promoter primer is an important and novel composition, the nature of which is described and defined in the present application. For example, paragraph [0522] of the present application defines a "promoter primer" as follows:

> '*A "promoter primer" is a primer, generally with a free 3'-OH group, that comprises a sequence that is complementary to a target sequence at its 3'-end and which encodes a transcription promoter in its 5'-portion.*' (paragraph [0522] of the published application)

Paragraph [0523] of the specification clarifies that, with respect to the embodiment of Claim 190, the transcription promoter in the 5'-portion of the promoter primer exhibits a "sense promoter sequence", as follows:

'*In embodiments of the invention in which a transcription substrate of the invention comprises first-strand cDNA obtained by reverse transcription or primer extension of a promoter primer using a target nucleic acid as a template, the transcription promoter in the promoter primer comprises a sense promoter sequence that is located in the 5'-portion of the promoter primer.*'
(paragraph [0523] of the published application)

The present application provides embodiments of methods that use either single-stranded promoters (e.g., a single-stranded promoter for N4 mini-vRNAP or single-stranded pseudopromoter for a T7-type RNAP) or double-stranded promoters (e.g., a double-stranded promoter for a T7-type RNAP).

The specification defines what is meant by a "sense promoter sequence" with respect to both of types of embodiments. For example, with respect to embodiments comprising single-stranded promoters, the present specification discusses a method '*to add a single-stranded **sense** promoter for an N4 mini-vRNAP to the 3'-end of a first-strand cDNA comprising a target sequence.*' (paragraph [0451] of the published application)

With respect to methods that use double-stranded promoters, the specification further states:

'*As defined herein, a **"sense promoter sequence" for a double-stranded promoter means the promoter sequence of an operable double-stranded promoter that is joined to the 3'-end of the template strand that is transcribed**, and an "anti-sense promoter sequence" is a sequence that is complementary to the sense promoter sequence.*"
(paragraph [0451] of the published application)

Therefore, according to the present specification with respect to methods that use either a single-stranded promoter or a double stranded-promoter, a sense promoter primer exhibits a 'sense promoter sequence', which the specification clearly defines as meaning the promoter sequence 'that is joined to the 3'-end of the template strand that is transcribed' (e.g., paragraph [0451] of the specification)

Still further, paragraph [0523] defines a problem that the method of claim 190 solves with respect to using a sense promoter primer, as follows:

> '*Thus, the transcription promoter in the linear first-strand cDNA obtained by reverse transcriptase- or DNA polymerase-catalyzed extension of the promoter primer using the target nucleic acid as a template is not operable as a promoter for transcription of the target sequence since the promoter is not operably joined to the 3'-end of the target sequence. A method of the present invention solves this problem by operably joining the single-stranded sense transcription promoter in the 5'-portion of the linear first-strand cDNA to the 3'-end of the target sequence using a ligase or another joining means, thus forming a circular ssDNA transcription substrate for an RNA polymerase that can bind the single-stranded promoter and transcribe the target sequence joined thereto.*'
> (paragraph [0523] of the specification)

A sense promoter primer is a defined term (in the present application) and an oligonucleotide used as a sense promoter primer in a method of the present claims must comply with the definition in the present application. A sense promoter primer is not a primer that synthesizes sense RNA; it is a primer that exhibits a sense promoter sequence in its 5'-portion. Methods exist in the prior art that synthesize sense RNA, but those prior art references did not use a sense promoter primer to do so.

The claimed method is new and not obvious from the methods previously known in the art is because it shows how to use a sense promoter primer to amplify a target nucleic acid sequence to which the 3'-portion of the sense promoter primer anneals and is extended by a DNA polymerase, including an RNA-dependent DNA polymerase or reverse transcriptase.

In order to emphasize the importance of the sense promoter primer, reference is made to Figure 20 of the present application, which is reproduced below for the Examiner's convenience.

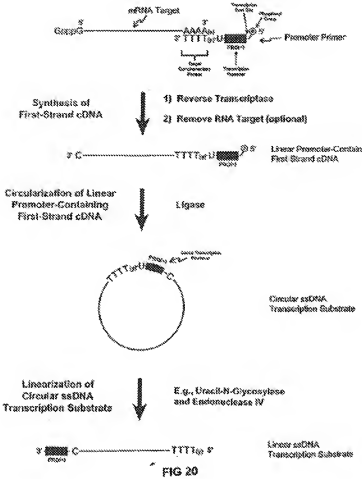

FIG 20

The uppermost diagram in Figure 20 shows one embodiment of a sense promoter primer that is annealed to an mRNA target nucleic acid. After synthesis of first-strand cDNA by extension of the sense promoter primer that is annealed to the mRNA template (e.g., by reverse transcription using an RNA-dependent DNA polymerase), a linear sense promoter-containing first-strand cDNA is obtained. It is important to note that this linear sense promoter-containing first-strand cDNA could not be used as a template for transcription by an RNA polymerase. Incubating such a template with an RNA polymerase that binds to the RNA polymerase promoter would not yield any product complementary to the template strand. This is because the sense promoter sequence is joined to the wrong end of the template for transcription. In order to be operable as an RNA polymerase promoter, the sense promoter sequence must first be operably joined to the 3'-end of the template strand sequence that is transcribed. Therefore, an RNA polymerase that recognizes the promoter will bind to the resulting promoter in the linear

sense promoter-containing first-strand cDNA, but it will not be able to transcribe the first-strand cDNA template because it is joined to the 5'-end of that template rather than to its 3'-end. Thus, one important aspect of the claimed method is the step of covalently joining the sense promoter sequence in the linear sense promoter-containing first-strand cDNA to the 3'-end of the template strand by ligating its 5'-end to its 3'-end, as shown in the next step in Figure 20. Thus, the use of the ligation step to operably join the sense promoter sequence to the 3'-end of the primer extension product is a novel and non-obvious aspect of the claimed method. Figure 20 also shows that, in some embodiments, the circular transcription substrate can be linearized at a cleavage site located 3'-of the sense promoter sequence, such as the dUMP cleavage site shown here, in order to generate a linear transcription substrate that correctly exhibits the sense promoter sequence 3'-of the template strand that is transcribed by the RNA polymerase.

Prior to the present application, there was a failure of others to recognize this method for operably joining the sense promoter sequence to the 3'-end of the primer extension product so that it would serve as the template for transcription. This explains why only anti-sense promoter primers had been used to amplify target nucleic acid sequences prior to the present application. Those who developed the methods in the prior art had shown that if an anti-sense promoter primer that is annealed to a target nucleic acid sequence is extended using a DNA polymerase and then the linear anti-sense promoter-containing first-strand cDNA is made double-stranded by extending an RNA or DNA primer that anneals to the linear anti-sense promoter-containing first-strand cDNA, the resulting second-strand cDNA will have a sense promoter sequence joined to its 3'-end. Then, the second-strand cDNA with the sense promoter sequence joined to its 3'-end in the resulting double-stranded cDNA will serve as a template for transcription by an RNA polymerase that binds the double-stranded promoter. Thus, all of the methods in the prior art used an anti-sense promoter primer rather than a sense promoter primer to amplify a target nucleic acid sequence. The RNA synthesized was *anti-sense with respect to the target nucleic acid sequence* to which the anti-sense promoter primer annealed. Therefore, prior to the present application, it was not known how to use a sense promoter primer to amplify a target nucleic acid sequence to generate RNA that was sense with respect to the target nucleic acid sequence in a sample. For example, it was not known how to use a sense promoter primer to generate transcripts that exhibit a nucleic acid sequences which are identical to one or multiple target RNA molecules in a sample, such as all of the mRNA molecules in a sample.

The above description also explains why anti-sense promoter primers, which exhibit an anti-sense promoter sequence in their 5'-portion, were well known in the prior art, whereas sense promoter primers were not known. It is noted that anti-sense promoter primers were used in many of the prior art methods for amplifying target nucleic acid sequences, such as in the transcription- based methods listed, referenced or described in paragraphs [0128] and [0306] of the present application. Examples of methods in the prior art which use anti-sense promoter oligos include Kurn's Ribo-SPIA™ methods, continuous amplification reaction (CAR), nucleic acid sequence-based amplification (NASBA), transcription-mediated amplification (TMA), 3SR, and the so-called "Eberwine aRNA amplification method."

None of the references cited by the Examiner (Kurn, Dai et al., Kacian, Ginsberg et al., or Diegelman et al.) teaches a method for using a sense promoter primer to make a transcription substrate. Prior to the presently claimed method, none of the references in the art, including the references cited by the Examiner, disclosed a composition comprising a sense promoter primer or showed how to use a sense promoter primer to generate a transcription substrate.

In point 11 on page 12 of the Office Action, the Examiner stated that Applicants' previous argument to traverse the rejection of Claim 190 was not persuasive because Kurn taught primers which hybridize to the sense strand of DNA. As discussed above, a sense promoter primer has a specific meaning according to the present specification. An oligonucleotide used as a sense promoter primer in a method of the present claims must comply with the definition in the present application. As such, a sense promoter primer must exhibit a sense promoter sequence in its 5'-portion. The mere fact that a primer would hybridize to the sense strand of DNA does not make it a sense promoter primer with respect to the presently claimed methods and does not comply with the meaning of a sense promoter primer in the present specification. A sense promoter primer according to the presently claimed method can hybridize to any strand of any target nucleic acid. It is a sense promoter primer because it is a primer that comprises a 5'-portion that exhibits a sense promoter sequence (but not if it exhibits an anti-sense promoter sequence). Thus, the Applicants respectfully ask the Examiner to remove the rejection of Claim 190 as amended, as well as the dependent claims based thereon.

Claims 191 and 192 are dependent on Claim 190. Claim 191 is currently amended to be consistent with independent Claim 190 as currently amended.

IV. New Claims

The Applicants have submitted new dependent Claims 206-214 which are dependent on amended independent Claim 190, and all of which are supported in the specification as filed:

New dependent Claim 206 is supported by paragraph [0522] of the specification.

New dependent Claim 207 is supported by paragraph [0527] of the specification.

New dependent Claims 208 and 209 are supported by paragraph [0531] of the specification.

New dependent Claims 210 and 211 are supported by paragraph [0528] of the specification.

New dependent Claim 212 is supported by paragraphs [0337] and [0632] of the specification.

New dependent Claim 213 is supported by paragraph [0636] of the specification.

New dependent Claim 214 is supported by paragraph [0787] of the specification.

New independent Claim 215 is an embodiment of the invention that is related to the above claims which use a sense promoter primer, but which embodiment also takes into account additional disclosures of the present application. This method embodiment is supported by the disclosures in the present application as published related to the method of claim 190 above which uses a sense promoter primer, as well as additional disclosures in the application, including:

paragraph [0359], which defines a 'primer';

paragraph [0609], which discusses that '*other oligos used in a method of the invention, including those that lack a promoter sequence, such as' ...'primers can have one or more of any of these additional sequences and/or genetic elements* (as discussed in paragraph [0609]) *5'-of the target-complementary or target-joining portion of each respective oligo.*';

paragraph [0636], which discloses that a method can be performed in a stepwise fashion by purifying the reaction products by removing reaction components and/or inactivating enzymes from one set of reactions prior to proceeding to the next set of reactions; and

paragraph [0354], which states that: '*The methods of the present invention can also be extended to analysis of sequence alterations and sequencing of the target nucleic acid.*'

In addition, the Applicants have submitted new dependent Claims 216-219 which are dependent on Claim 215, all of which are supported in the specification as filed:

New dependent Claim 216 is supported by paragraph [0337] of the specification.

New dependent Claim 217 is supported by paragraph [0373] of the specification.

New dependent Claim 218 is supported by paragraph [0373] of the specification.

New dependent Claim 219 is supported by paragraph [0362] of the specification.

V. Cross-Noting Related Application

Applicants wish to bring to the Examiner's attention related application 10/719,913, which contains claims that include a sense promoter primer. The Examiner can find the prosecution history of this application on PAIR. If the Examiner would rather receive a part of, or all of, the prosecution history of this related application (and the cited references) please let Applicants know and this will be provided by Applicants.

CONCLUSION

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned at 608-218-6900.

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